REMARKS

Reconsideration is respectfully requested. Claims 21-34 were previously pending in the application. Accordingly, claims 21-34 are pending in the application.

1.132 Declaration of Dr. James Shen

Applicants respectfully request entry of the Declaration of Dr. James Shen provided herewith. The copy provided is an original, so it should be legible upon scanning into the USPTO database.

Claim Rejections – 35 U.S.C. § 102

Claims 21, 23-27, and 30-32 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Zhang et. al., JBC 270: 8501-8505 (1995) ("Zhang 1995").

Applicants respectfully traverse the rejection and its supporting remarks. The Examiner has asserted that:

> Furthermore even though the cited art suggested the transient transfection of genetic material it is know in the art that transfection of plasmids into host cells often results in the chromosomal integration of genetic material in the cells, which could be easily detected upon the selection of the genetically modified cells. Thus given the broadest reasonable interpretation the cited art clearly anticipate the invention as claimed.

The Examiner has asserted that it is well known in the art that plasmids integrate into host cells. Given that the claims are to human cells, the Examiner must have meant human host cells. The applicants are unaware of any art that would support the assertion that a construct in a transient transfection assay in human cells would integrate with a sufficient frequency to produce an isolated animal cell as presently claimed. The Examiner in the Advisory Action has asserted that the reference cited in the Declaration submitted herewith is contradictory because he alleges it provides evidence that constructs can integrated during transient transfections; however, as further

discussed below and in the Declaration of Dr. Shen, the length of time of that the transiently transfected cells were used in the Zhang et al. reference was too short a time for integration to have occurred. Thus the Applicants maintain that they are unaware of any reference that would support that the transient assay conducted in the 1995 Zhang reference would lead to integration, both because the time of the assays was too short and as discussed in the Declaration of Dr. Shen, the integration frequency even if the cells are maintained long enough for integration to occur is too low to constitute "***isolated***" cells. Applicants respectfully traverse this assertion and request that the Examiner provide references that demonstrate a sufficiently high rate of integration that the techniques used in the 1995 Zhang reference would yield "***isolated*** animal cell whose genomic DNA comprises at least one copy of a ***chromosomally*** integrated transgene" as presently claimed so that the applicants can better understand the Examiner's argument. MPEP § 2144.03 "If the applicant traverses such an assertion the examiner should cite a reference in support of his or her position."

In fact, it is applicants' understanding that integration into mammalian cells such as human cells occurs at a very low frequency. This was discussed previously in regard to generating transgenic animals (see the Declaration of Dr. James Shen submitted on December 1, 2003 wherein he stated "The efficiency of integration using this method [pronuclear injection] was and still is low, but that low efficiency is simply part of the overall protocol and is well accepted and understood in the art"). Thus, there is declaratory evidence already of record contrary to the Examiner's unsupported assertion. For the avoidance of doubt, pronuclear injection is a different method than the transient transfection assay. Pronuclear injection is a method aimed at getting a genetic construct to integrate into the genome, so it includes maintaining the cells in culture for a long enough period of time to allow integration unlike a transient transfection assay. Thus, even when the protocol is specifically designed to achieve integration of a genetic construct into integrate into the genome, the frequency of integration is low.

In addition, the Declaration of Dr. Shen submitted herewith further supports the low frequency of integration even citing to a reference which provides an estimate of the frequency of integration. Furthermore, Dr. Shen states in his Declaration that the random integration would not

have occurred within the time period of the transient transfection assay. Thus, the Zhang 1995 reference does not teach the element of an "***isolated*** animal cell whose genomic DNA comprises at least one copy of a ***chromosomally*** integrated transgene ..." because it is likely that none of the constructs integrated. Even if the cells were maintained longer than the transient transfection assays taught in Zhang 1999 and thereby the construct might have integrated in a small fraction of the cells, potentially having one cell with a chromosomally integrated construct in a larger population cells with only transient expression could hardly be considered "***isolated***" within the scope of the claims.

The Examiner's assertion that cells with the constructs chromosomally inserted could be readily selected for is irrelevant and suggests that the Examiner recognizes that such cells are not "***isolated***." This is a modification of the reference that is not taught or suggested in the reference and therefore could only be asserted in a 103(a) rejection. Furthermore, in order to select for the chromosomal integration, the construct must have a marker that is selectable in eukaryotes. There is no marker in the constructs used in the Zhang 1995 reference that could have served as a selectable marker. This is supported by the Declaration of Zhang *et al.* submitted herewith.

In order to anticipate a claim under 35 U.S.C. § 102(b), a reference must teach each and every element of a claimed invention. MPEP 2131. As discussed above, the Zhang 1995 reference fails to teach each and every element of the claimed invention, specifically the Zhang 1995 reference fails to teach an "***isolated*** animal cell whose genomic DNA comprises at least one copy of a ***chromosomally*** integrated transgene." As stated above, the construct would not have integrated in the time of the transient transfection assay, so this element has not been met. Thus, this requirement for maintaining a rejection under 35 U.S.C. § 102(b) is not met by the Zhang 1995 reference, and Applicants respectfully request that this ground for rejection be withdrawn.

Claim Rejections – 35 U.S.C. § 103

Claims 22, 28-29, and 33-34 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Zhang 1995, as applied to claims 21-27 and 30-32, and further in view of Zhang et al., Mol Cell Biol., 4:2298-308, 1993 ("Zhang 1993").

Applicants respectfully traverse these grounds for rejection. In order to establish a *prima facie* case of obviousness, an examiner must meet three basic criteria: (1) there must be some suggestion or motivation to modify a reference or combine reference teachings, (2) there must be a reasonable expectation of success, (3) the references must teach or suggest all claim limitations. MPEP 2142.

Even if a *prima facie* case of obviousness has been established, a *prima facie* case of obviousness may be rebutted by a showing of superior or unexpected results. MPEP 2144.09. The applicants made such a showing in the previous response submitted on August 1, 2005 response. The Examiner did not mention or refute that showing in the final Office Action sent on October 19, 2005. As discussed in the applicants' previous response, the TCTGAGTCA (SEQ ID NO:1) sequence when used in a chromosomally integrated expression construct shows superior and unexpected results by over coming previous limitations associated with expression of chromosomally integrated constructs (e.g., position-effect variegation, silencing of transgenes, and the inability to increase expression by increasing gene copy number). See, e.g., Sabl et al., Genetics 142:447-458 (1996); Palmer et al., Sharpe et al., EMBO J 11:4565-4572 (1992); and Chen et al., Proc. Natl. Acad. Sci. USA 94:5798-5803 (1997). This is clearly an unexpected result as shown in Table 1 of the specification. Table 1 shows that when the mutant HS-40 transgene is used, a strong positive correlation between copy number of the transgene and hGH expression is observed; in contrast, when the wild type HS-40 transgene is used, increased expression of hGH is not consistently observed with increased copy number. The fact that the wild-type HS-40 element does not provide such position independent expression proves that one of skill in the art would not expect that the presently claimed mutant HS-40 element would provide this result especially given that the wild-type HS-40 element is the closest available enhancer element to the mutant HS-40 presently

claimed. Dr. Shen further supports the assertion that this result is unexpected in his Declaration submitted herewith.

As discussed regarding the enablement rejection previously withdrawn by the Examiner, the unexpected result is commensurate with the scope of the pending claims (see pages 7-8 of Applicant's response submitted on December 1, 2003 for a full discussion of the scope of enablement). Dr. Shen in his Declaration submitted on December 1, 2003 provided an abundance of evidence supporting the assertion that DNA elements that provide position independent expression act across the animal kingdom and elements from one species will function in widely divergent animal species. Thus, the position independent expression observed with the presently claimed mutant HS-40 element (from a chicken gene that functions in both pig and mouse) will provide the unexpected result commensurate in scope with the present claims.

Finally, the unexpected result is included in the presently pending claims. Therefore, even if the Examiner has established a *prima facie* case of obviousness, this unexpected result would rebut any such claim. The Examiner did not address this part of the applicants' last response in the final Office Action dated October 19, 2005. Applicants respectfully request that the Examiner withdraw the rejection of claims 22, 28-29, and 33-34 based upon 35 U.S.C. § 103(a) given that the claimed invention provides unexpected results.

The Examiner has asserted that it would not be unexpected that the mutant HS-40 element provides position independent expression. However, the specification clearly indicates that the wild-type HS-40 does not provide position independent expression, so one of skill in the art could not expect that the mutant HS-40 as claimed provides position independent expression. It is irrelevant that other elements exist that provide position independent expression. The question is whether the position independent expression provided by the claimed invention is unexpected, which it is.

In addition, as discussed above in regard to the 35 U.S.C. § 102(b) rejection, neither Zhang 1995 nor Zhang 1993 teach an "***isolated*** animal cell whose genomic DNA comprises at least

one copy of a ***chromosomally*** integrated transgene" as is presently claimed. Applicants respectfully request that the Examiner withdraw the rejection of claims 22, 28-29, and 33-34 based upon 35 U.S.C. § 103(a) given that the references fail to teach or suggest an element of the present claims.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 514162000120. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

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